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(54) MEDICINAL COMPOSITIONS CONTAINING ASPIRIN

ASPIRIN ENTHALTENDE MEDIZINISCHE ZUSAMMENSETZUNGEN

COMPOSITIONS MEDICALES CONTENANT DE L'ASPIRINE

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Description

[TECHNICAL FIELD]

[0001] This invention relates to pharmaceutical compositions containing 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, as active ingredients [particularly pharmaceutical compositions for prevention or treatment (particularly for treatment) of diseases caused by thrombus or embolus]; to the use of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and aspirin for the manufacture of pharmaceutical compositions for prevention or treatment (particularly for treatment) of diseases caused by thrombus or embolus; and to methods for the prevention or treatment (particularly to methods for the treatment) of diseases caused by thrombus or embolus by administration of an effective amount of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and aspirin to warm-blooded animals (particularly humans).

[BACKGROUND ART]

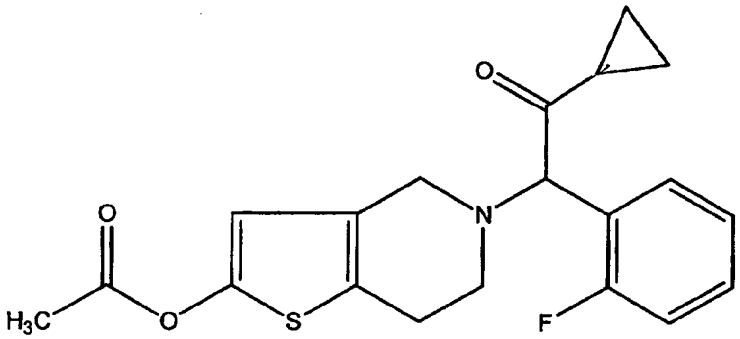
[0002] 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine has been described in the Japanese Patent Application Publication No. Hei 6-41139, and possesses potent inhibitory activity against platelet aggregation. Furthermore, aspirin is well known to have an inhibiting activity against platelet aggregation, although the activity is low. However, pharmaceutical compositions containing both compounds have not been known.

[DISCLOSURE OF THE INVENTION]

[0003] The present inventors have studied therapeutic agents with low toxicity that exert inhibitory activity against platelet aggregation and have found that the problems described above are solved by using pharmaceutical compositions comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and aspirin.

[0004] The present invention provides pharmaceutical compositions containing 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and aspirin as active ingredients [particularly pharmaceutical compositions for prevention or treatment (particularly for treatment) of diseases caused by thrombus or embolus]; the use of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, for the manufacture of pharmaceutical compositions [particularly pharmaceutical compositions for prevention or treatment (particularly for treatment) of diseases caused by thrombus or embolus]; and methods for the prevention or treatment (particularly methods for treatment) of diseases caused by thrombus or embolus by administration of an effective amount of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, to warm-blooded animals (particularly humans), simultaneously or sequentially.

[0005] 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine, and pharmaceutically acceptable salts thereof, which is one of the active ingredients of the present invention, is a known compound. For instance, the compound has already been described in Japanese Patent Application Publication No. Hei 6-41139 and Japanese Patent Application Publication No. 2002-145883 (priority: Japanese Patent Application No. 2000-205396 and Japanese Patent Application No. 2000-266780). The chemical structure is described below.



[0006] The pharmaceutically acceptable salts of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine may be, for example, hydrohalogenic acid salts such as hydrofluoride, hydrochloride, hydrobromide or hydroiodide; nitrate; perchlorate; sulfate; phosphate; C_1-C_4 alkanesulfonates optionally substituted by halogens such as methanesulfonate, trifluoromethanesulfonate, ethanesulfonate; C_6-C_{10} arylsulfonates optionally substituted by C_1-C_4 alkyl groups such as benzenesulfonate or p-toluenesulfonate; C_1-C_6 aliphatic acid salts such as acetate, malate, fumarate, succinate, citrate, tartarate, oxalate or maleate; amino acid salts such as glycine salt, lysine salt, arginine salt, omitine salt, glutamic acid salt or aspartic acid salt; and the preferred compounds are hydrohalogenates or C_1-C_6 aliphatic acid salts; and more preferred compounds are the hydrochloride or the maleate.

[0007] When one of the active ingredients of the present invention, 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, is allowed to stand so that it is open to the atmosphere, it may become hydrated by absorption of water or adsorption of water. Such hydrated compounds are included in the present invention.

[0008] Further, one of the active ingredients of the present invention, 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, may absorb some kinds of organic solvents and may form solvates in some cases, and these solvates are also included in the present invention.

[0009] Furthermore; since 2-aeetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine has an asymmetric carbon atom, optical isomers exist based on the asymmetric carbon atom. These optical isomers are also included in the present invention.

[0010] The other active ingredient, aspirin, is a well-known compound, as an analgesic antipyretic.

[INDUSTRIAL APPLICABILITY]

[0011] The pharmaceutical compositions of the present invention (particularly pharmaceutical compositions for the prevention or treatment of diseases caused by thrombus or embolus) which contain 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, as active ingredients, possess excellent inhibitory activity against platelet aggregation and thrombogenesis with short onset latency and low toxicity. Thus the pharmaceutical compositions of the present invention are useful as preventative or therapeutic agents (particularly as therapeutic agents) against diseases caused by thrombus or embolus, for example, diseases induced by platelet aggregation, including stable or unstable angina pectoris and so forth; cardiovascular or cerebrovascular disorders, e.g., thromboembolism, associated with atherosclerosis or diabetes mellitus, such as unstable angina pectoris, cerebral ischemic insult or restenosis due to angioplasty, endarterectomy or stent therapy; or thromboembolism caused by thromboembolization such as recurrent embolism after degradation of the original thrombus, embolism, ischemia-induced dementia, peripheral arteriopathy, thromboembolization associated with hemodialysis or atrial fibrillation, or thromboembolization in the vascular prosthesis, or in the bypass between the aorta and the coronary artery. Furthermore, the therapeutic agent of the present invention is administered to warm-blooded animals (particularly humans).

[0012] According to the present invention, the use in combination of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, results in more potent effectiveness than the use of each component alone. Furthermore, plasma levels of these agents do not have to be maintained at a certain level and higher during the same period, in order to produce their effects. It is believed that these 2 agents reach the receptors, at which they act *in vivo,* and turn on switches at the receptors to induce the effects. Even though the plasma level of one component of the pharmaceutical composition is too low to induce the effects with

increasing time after the agent was administered, the switches at the receptors have already been turned on. Thus the preventative or therapeutic efficacy of the agent is expected by inhibiting thrombogenesis or embolization.

[0013] Therefore, when the other component of the pharmaceutical composition is administered later, the therapeutic effect of the compound administered later is expected to add to the therapeutic effects of the previously administered component. However, it is convenient clinically that both components are administered at the same time. Thus 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof and aspirin are simultaneously administered as a combination drug. In the case that both agents cannot be mixed technically, each component can be administered separately. Moreover, as described previously, since each component produces significant effects as a single form, each component can be sequentially administered at appropriate intervals. The maximum intervals between administration of each of the two components that can be accepted to elicit significant effects could be confirmed by clinical trials or animal studies.

[0014] The route for administration of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, which is employed in the present invention, is generally the oral route. However, other routes, for example, intravenous administration, can be used. Thus, the 2 components can be prepared respectively as separate formulations, or can be mixed physically to form a single formulation for administration. The single formulations of the mixed components are, for example, powders, granules, tablets, capsules and so forth, and can be prepared by regular formulation techniques, as described below.

[0015] These formulations are prepared by conventional methods by using excipients (organic excipients, for example, sugar derivatives such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives such as corn starch, potato starch, α-starch or dextrin; cellulose derivatives such as crystalline cellulose; gum arabic; dextran; or pullulan; and inorganic excipients, for example, silicate derivatives such as light silicic acid anhydride, synthetic aluminum silicate, calcium silicate or magnesium aluminate metasilicate; phosphate derivatives such as calcium hydrogenphosphate; carbonates such as calcium carbonate; or sulfates such as calcium sulfate), lubricants (for example, stearic acid; metal stearate derivatives such as calcium stearate or magnesium stearate; talc; waxes such as beeswax or spermaceti; boric acid; adipic acid; sulfate derivatives such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; lauryl sulfate derivatives such as sodium lauryl sulfate or magnesium lauryl sulfate; silicic acid derivatives such as silicic acid anhydride or silicic acid hydrate; and starch derivatives described above), binders (for example, hydroxypropyl cellulose, hydroxypropylmethylcellulose, poly(vinylpyrrolidone), polyethylene glycol and similar compounds described in the above excipients), disintegrators (for example, cellulose derivatives such as low substituted hydroxypropylcellulose, carboxymethylcellulose, calcium carboxymethylcellulose, internally cross-linked sodium carboxymethylcellulose; chemically modified starch/cellulose derivatives such as carboxymethylstarch, sodium carboxymethylstarch; cross-linked polyvinylpyrrolidone; or starch derivatives described above), emulsifiers (for example, colloidal clays such as bentonite or veegum; metal hydroxides such as magnesium hydroxide or aluminum hydroxide; anionic surfactants such as sodium lauryl sulfate or calcium stearate; cationic surfactants such as benzalkonium chloride; or nonionic surfactants such as polyoxyethylene alkyl ether, polyoxyethylenesorbitan ester of fatty acids or sucrose ester of fatty acids), stabilizers (for example, parahydroxybenzoates such as methylparaben or propylparaben; alcohols such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chlorides; phenol derivatives such as phenol or cresol; thimerosal; dehydroacetic acid; or sorbic acid), corrigents (for example, sweetening, souring and flavoring agents all of which are conventionally used), and diluents.

[0016] The dose and the dose ratio of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno [3,2-c]pyridine or pharmaceutically acceptable salt thereof, and aspirin, can be widely altered based on several factors such as activity of each compound, and the symptoms, age and body weight of the patients.

[0017] Generally, the lower limit of the oral dose (mg drug dose/time) is 0.1 mg (preferably, 1 mg) per time, while the upper limit is 1,000 mg (preferably, 500 mg) per time. The lower and upper limits of intravenous injection are 0.01 mg (preferably, 0.1 mg) and 500 mg (preferably, 250 mg), respectively. They are administered to the adult from 1 to 7 times a day based on the symptoms of the patient, simultaneously or sequentially.

[0018] Generally, the dose ratio of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or pharmaceutically acceptable salt thereof, and aspirin, is from 1:500 to 500:1 as their weight ratio.

[Best Mode for Carrying Out the Invention]

[0019] The present invention is described in detail with examples and formulations in the following. However, the claim of the present invention is not restricted to the following description.

(Example 1)

Inhibitory Activity against Thrombogenesis

[0020] As the test animals, male Sprague Dawley rats of 7 weeks old were purchased from SLC Japan and 6 rats per group were used.

[0021] 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine was synthesized according to the method described in the Specification of Japanese Patent Application Publication No. Hei 6-41139 and was used, while aspirin was purchased from Sigma Chemical Co. and was used. Both compounds were suspended in 5% (w/v) gum arabic solution, and were diluted so as to be 1 ml/kg of administration volume and were orally administered.

[0022] The inhibitory activities of the compounds against thrombogenesis or thrombus formation were evaluated in the modified arterio-venous shunt thrombosis model in rats, which was described by Umetsu et al. [Thromb. Haemost., 39, 74-83 (1978)].

[0023] The shunt tube was prepared as follows; i.e., both sides of a medical silicon tube of 12 cm length [inner diameter: 1.5 mm, outer diameter: 2.5 mm, purchased from KANEKA Medix Co., Ltd] were connected each to a polyethylene tube of 7 cm length [inner diameter: 0.5 mm, outer diameter: 1.0 mm, purchased from Natsume Seisakusho Co., Ltd.] covered with silicon via a medical silicon tube of 0.7 cm length [inner diameter: 1.0 mm, outer diameter: 1.5 mm, KANEKA Medix Co., Ltd] as connector. A surgical suture of 10 cm length was placed in the silicon tube of 12 cm length.

[0024] The animal was anesthetized with an intraperitoneal injection of 40 mg/kg of pentobarbital sodium (purchased from Abbott Laboratories Inc.), and the jugular of one side and the carotid of the other side were exposed. The arterio-venous shunt was made by cannulation of a shunt tube filled with heparin solution [30 units/kg, purchased from Fuso Pharmaceutical Co., Ltd] into the carotid and the jugular which had been previously exposed.

[0025] The test compounds were orally administered and the blood was started to circulate into the shunt area two hours after the administration. Thirty minutes after the circulation was started, the shunt tube was removed, and the thrombus adsorbed on the surgical suture was weighed. The results are shown in Table 1. The results in the table are expressed as the average weight ± SE (n=6).

[Table 1]

Compounds		Thrombus Weight	Inhibition Rate
Compound A (mg/kg)	Aspirin (mg/kg)	(mg)	(%)
0	0	52.3 ± 1.2	-
0	10	46.6 ± 2.8	12.3 ± 4.4
0.3	0	43.5 ± 2.1	17.0±4.1
0.6	0	37.5±2.1	28.3 ± 4.0
0.3	10	30.5 ± 3.5	41.8 ± 6.6
0.6	10	23.2 ±3.8	55.7 ±7.2

Compound A: 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine

(Formulation 1)

[0026]

Tablets	
Compound A	10.0 mg
Aspirin	12.5 mg
Lactose	175.5 mg
Corn starch	50.0 mg
Magnesium stearate	2.0 mg
Total	250 mg

[0027] The powders in the formula described in the above table are mixed, compressed with a tableting machine and formulated as a tablet containing 250 mg in total. The tablet can be coated with film or sugar, when necessary.

Claims

1. A pharmaceutical composition comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, as active ingredients.

2. A pharmaceutical composition according to claim 1, in which the pharmaceutically acceptable salt is the hydrochloride or maleate.

3. A pharmaceutical composition according to claim 1 or claim 2, in which the composition is used for preventing or treating diseases caused by thrombus or embolus.

4. A pharmaceutical composition according to claim 1 or claim 2, in which the composition is used for preventing or treating diseases caused by thrombus or embolus in warm-blooded animals.

5. A pharmaceutical composition according to claim 1 or claim 2, in which the composition is used for preventing or treating diseases caused by thrombus or embolus in humans.

6. A kit comprising 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, for simultaneous or sequential administration.

7. A kit according to claim 6, for simultaneous administration.

8. A kit according to claim 6, for sequential administration.

9. A kit according to any of claims 6 to 8, in which the pharmaceutically acceptable salt is the hydrochloride or maleate.

10. A kit according to any of claims 6 to 9, which is used for preventing or treating diseases caused by thrombus or embolus.

11. A kit according to any of claims 6 to 9, which is used for preventing or treating diseases caused by thrombus or embolus in warm-blooded animals.

12. A kit according to any of claims 6 to 9, which is used for preventing or treating diseases caused by thrombus or embolus in humans.

13. Use of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof, and aspirin, in the preparation of a medicament for the prevention or treatment of diseases caused by thrombus or embolus.

14. Use of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof in the preparation of a medicament for the prevention or treatment of diseases caused by thrombus or embolus, wherein said prevention or treatment also comprises the simultaneous or sequential administration of aspirin.

15. Use of aspirin in the preparation of a medicament for the prevention or treatment of diseases caused by thrombus or embolus, wherein said prevention or treatment also comprises the simultaneous or sequential administration of 2-acetoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridine or a pharmaceutically acceptable salt thereof.

16. Use according to any of claims 13 to 15, in which the pharmaceutically acceptable salt is the hydrochloride or maleate.

17. Use according to any of claims 13 to 16, wherein the medicament is used for preventing or treating diseases caused by thrombus or embolus.

18. Use according to any of claims 13 to 16, wherein the medicament is used for preventing or treating diseases caused by thrombus or embolus in warm-blooded animals.

19. Use according to any of claims 13 to 16, wherein the medicament is used for preventing or treating diseases caused

by thrombus or embolus in humans.

20. Use according to any of claims 14 to 19, wherein the administration is simultaneous.

21. Use according to any of claims 14 to 19, wherein the administration is sequential.

Patentansprüche

1. Pharmazeutische Zusammensetzung, aufweisend 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin oder ein pharmazeutisch akzeptables Salz davon und Aspirin als Wirkstoffe.

2. Pharmazeutische Zusammensetzung nach Anspruch 1, worin das pharmazeutisch akzeptable Salz das Hydrochlorid oder Maleat ist.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin die Zusammensetzung zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus hervorgerufen werden.

4. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin die Zusammensetzung zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Warmblütern hervorgerufen werden.

5. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, worin die Zusammensetzung zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Menschen hervorgerufen werden.

6. Kit, aufweisend 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin oder ein pharmazeutisch akzeptables Salz davon sowie Aspirin zur gleichzeitigen oder aufeinanderfolgenden Verabreichung.

7. Kit nach Anspruch 6 zur gleichzeitigen Verabreichung .

8. Kit nach Anspruch 6 zur aufeinanderfolgenden Verabreichung.

9. Kit nach einem der Ansprüche 6 bis 8, wobei das pharmazeutisch akzeptable Salz das Hydrochlorid oder Maleat ist.

10. Kit nach einem der Ansprüche 6 bis 9, das zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus hervorgerufen werden.

11. Kit nach einem der Ansprüche 6 bis 9, das zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Warmblütern hervorgerufen werden.

12. Kit nach einem der Ansprüche 6 bis 9, das zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Menschen hervorgerufen werden.

13. Verwendung von 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin oder ein pharmazeutisch akzeptables Salz davon sowie Aspirin in der Herstellung eines Medikaments für die Verhütung oder Behandlung von Erkrankungen, die durch Thrombus oder Embolus hervorgerufen werden.

14. Verwendung von 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin oder eines pharmazeutisch akzeptablen Salzes davon in der Herstellung eines Medikaments für die Verhütung oder Behandlung von Erkrankungen, die durch Thrombus oder Embolus hervorgerufen werden, wobei die Verhütung oder Behandlung ebenfalls die gleichzeitige oder aufeinanderfolgende Verabreichung von Aspirin umfasst.

15. Verwendung von Aspirin in der Herstellung eines Medikaments für die Verhütung oder Behandlung von Erkrankungen, die durch Thrombus oder Embolus hervorgerufen werden, wobei die Verhütung oder Behandlung ebenfalls die gleichzeitige oder aufeinanderfolgende Verabreichung von 2-Acetoxy-5-(α-cyclopropylcarbonyl-2-fluorbenzyl)-4,5,6,7-tetrahydrothieno[3,2-c]pyridin oder eines pharmazeutisch akzeptablen Salzes davon umfasst.

16. Verwendung nach einem der Ansprüche 13 bis 15, wobei das pharmazeutisch akzeptable Salz das Hydrochlorid oder Maleat ist.

17. Verwendung nach einem der Ansprüche 13 bis 16, wobei das Medikament zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus hervorgerufen werden.

18. Verwendung nach einem der Ansprüche 13 bis 16, wobei das Medikament zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Warmblütern hervorgerufen werden.

19. Verwendung nach einem der Ansprüche 13 bis 16, wobei das Medikament zur Verhütung oder Behandlung von Erkrankungen verwendet wird, die durch Thrombus oder Embolus in Menschen hervorgerufen werden.

20. Verwendung nach einem der Ansprüche 14 bis 19, wobei die Verabreichung gleichzeitig erfolgt.

21. Verwendung nach einem der Ansprüche 14 bis 19, wobei die Verabreichung aufeinanderfolgend erfolgt.

Revendications

1. Composition pharmaceutique comprenant de la 2-acétoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tétrahydrothiéno[3,2-c]pyridine ou un sel pharmaceutiquement acceptable de celle-ci, et de l'aspirine, en tant qu'ingrédients actifs.

2. Composition pharmaceutique selon la revendication 1, dans laquelle le sel pharmaceutiquement acceptable est le chlorhydrate ou le maléate.

3. Composition pharmaceutique selon la revendication 1 ou la revendication 2, la composition étant utilisée pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus.

4. Composition pharmaceutique selon la revendication 1 ou la revendication 2, la composition étant utilisée pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez des animaux à sang chaud.

5. Composition pharmaceutique selon la revendication 1 ou la revendication 2, la composition étant utilisée pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez les humains.

6. Kit comprenant de la 2-acétoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tétrahydrothiéno[3,2-c]pyridine ou un sel pharmaceutiquement acceptable de celle-ci, et de l'aspirine, pour une administration simultanée ou successive.

7. Kit selon la revendication 6, pour une administration simultanée.

8. Kit selon la revendication 6, pour une administration successive.

9. Kit selon l'une quelconque des revendications 6 à 8, dans lequel le sel pharmaceutiquement acceptable est le chlorhydrate ou le maléate.

10. Kit selon l'une quelconque des revendications 6 à 9, qui est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus.

11. Kit selon l'une quelconque des revendications 6 à 9, qui est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez des animaux à sang chaud.

12. Kit selon l'une quelconque des revendications 6 à 9, qui est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez les humains.

13. Utilisation de 2-acétoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tétrahydrothiéno[3,2-c]pyridine ou d'un sel pharmaceutiquement acceptable de celle-ci, et d'aspirine, dans la préparation d'un médicament pour la prévention ou le traitement de maladies provoquées par un thrombus ou un embolus.

14. Utilisation de 2-acétoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tétrahydrothiéno[3,2-c]pyridine ou d'un sel pharmaceutiquement acceptable de celle-ci, dans la préparation d'un médicament pour la prévention ou le traitement de maladies provoquées par un thrombus ou un embolus, dans laquelle ladite prévention ou ledit traitement comprend aussi l'administration simultanée ou successive d'aspirine.

15. Utilisation d'aspirine dans la préparation d'un médicament pour la prévention ou le traitement de maladies provoquées par un thrombus ou un embolus, dans laquelle ladite prévention ou ledit traitement comprend aussi l'administration simultanée ou successive de 2-acétoxy-5-(α-cyclopropylcarbonyl-2-fluorobenzyl)-4,5,6,7-tétrahydrothiéno[3,2-c]pyridine ou d'un sel pharmaceutiquement acceptable de celle-ci.

16. Utilisation selon l'une quelconque des revendications 13 à 15, dans laquelle le sel pharmaceutiquement acceptable est le chlorhydrate ou le maléate.

17. Utilisation selon l'une quelconque des revendications 13 à 16, dans laquelle le médicament est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus.

18. Utilisation selon l'une quelconque des revendications 13 à 16, dans laquelle le médicament est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez des animaux à sang chaud.

19. Utilisation selon l'une quelconque des revendications 13 à 16, dans laquelle le médicament est utilisé pour prévenir ou traiter des maladies provoquées par un thrombus ou un embolus chez les humains.

20. Utilisation selon l'une quelconque des revendications 14 à 19, dans laquelle l'administration est simultanée.

21. Utilisation selon l'une quelconque des revendications 14 à 19, dans laquelle l'administration est successive.

REFERENCES CITED IN THE DESCRIPTION

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